Long-Term Efficacy and Safety of Tocilizumab Monotherapy in Patients with Rheumatoid Arthritis Previously Methotrexate Naive or Methotrexate Free for 6 Months Prior to Study Start

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RA treatment milestones

First reported use of MTX in RA\(^1\) (1951)

MTX in common use in RA\(^2\) (1985)

ACR criteria for RA classification\(^3\) (1987)

ACR treatment recommendations (2008)\(^5\)

New ACR/EULAR RA classification criteria (2010)\(^7\)

EULAR treatment recommendations (2010)\(^8\)

T2T recommendations (2010)\(^9\)

Updated ACR treatment recommendations (2012)\(^10\)

Future: JAK, SYK, IL-17 inh. Other IL-6/IL-6R inh.

Future: Biosimilars

Infliximab (2000)
Etanercept (2000)
Adalimumab (2003)

Rituximab (2006)

Tocilizumab (2009)

Anakinra (2002)

Abatacept (2007)

Golimumab, Certolizumab (2009)

Rituximab (2006)

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Future: JAK, SYK, IL-17 inh. Other IL-6/IL-6R inh.

Future: Biosimilars

For biologics, dates shown are for EU (EMA) approval for use in RA\(^4\)

Approximately a third of RA patients on biologics are on monotherapy.


All registries/studies are anti-TNF focused, other than ORA (abatacept), AIR (rituximab) and RABBIT (anti-TNFs and anakinra)

* MATRIX and LOHEN represents the proportion of the patients treated with a biologic agent without methotrexate (as a single agent or in combination with another DMARD)
Comparison of monotherapy trials: ACR20

The effect of bDMARD monotherapy on X-ray progression (Jones G, BTT 2012)

### Table 4: Biologic monotherapy versus methotrexate: standardized mean difference for total X-ray score

<table>
<thead>
<tr>
<th>Medication</th>
<th>Reference</th>
<th>Follow-up period</th>
<th>Number analyzed</th>
<th>SMD (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tocilizumab</td>
<td>Nishimoto et al(^1)(^8)</td>
<td>12 months</td>
<td>300</td>
<td>-0.43 (-0.65, -0.20)</td>
</tr>
<tr>
<td>Etanercept</td>
<td>Bathon et al(^5)</td>
<td>12 months</td>
<td>395</td>
<td>-0.28 (-0.48, -0.08)</td>
</tr>
<tr>
<td></td>
<td>Klareskog et al(^6)</td>
<td>12 months</td>
<td>424</td>
<td>-0.24 (-0.43, -0.05)</td>
</tr>
<tr>
<td></td>
<td><strong>Pooled</strong></td>
<td></td>
<td></td>
<td>-0.26 (-0.40, -0.12)</td>
</tr>
<tr>
<td>Adalimumab</td>
<td>Breedveld et al(^4)</td>
<td>12 months</td>
<td>531</td>
<td>-0.23 (-0.40, -0.05)</td>
</tr>
<tr>
<td>Golimumab</td>
<td>Emery et al(^1)(^5)</td>
<td>12 months</td>
<td>319</td>
<td>-0.02 (-0.24, +0.20)</td>
</tr>
<tr>
<td></td>
<td>GO-BEFORE(^1)(^5)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Emery et al(^1)(^5)</td>
<td>12 months</td>
<td>222</td>
<td>-0.04 (-0.30, +0.23)</td>
</tr>
<tr>
<td></td>
<td>GO-FORWARD(^1)(^5)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td><strong>Pooled</strong></td>
<td></td>
<td></td>
<td>-0.03 (-0.20, +0.14)</td>
</tr>
</tbody>
</table>
STREAM: Tocilizumab monotherapy over 5 years in Japan

- No general loss of response occurred during long-term treatment
  - Only 1 of 143 patients withdrew as a result of an unsatisfactory response
  - 87% reduced and 31% stopped prednisolone


Inclusion criteria (original study): DMARD-IR, active RA ≥6 mos, MTX ≥8 wks, ≥6 tender joints, ≥6 swollen joints, ESR of ≥30 mm/h and/or CRP of ≥10 mg/l
AMBITION – Actemra versus Methotrexate double-Blind Investigative Trial in mONotherapy

- Randomised, double-blind, double-dummy, multicentre Phase III study

Objective
- To evaluate the efficacy and safety of tocilizumab monotherapy vs methotrexate monotherapy in patients with active RA who had not previously failed methotrexate/biologics treatment

Adults with:

- Moderate to severe RA of ≥3 months’ duration
- Swollen joint count (SJC) ≥6 (of 66)
- Tender joint count (TJC) ≥8 (of 68)
- CRP ≥1.0 mg/dl and/or ESR ≥28 mm/h
- No current treatment with MTX or biologic therapy
  - If prior treatment, not treated for ≥6 months prior to randomisation and not failed for lack of efficacy or serious toxicity

CRP = C-reactive protein; ESR = erythrocyte sedimentation rate

AMBITION: primary results

Data shown for ACR responses at Week 24

† Lower limit of 95% CI for the difference vs. MTX was >0

AMBITION: DAS28 remission rate

Odds ratio (95% CI) = 5.8 (3.3–10.4)

AMBITON: DAS28 remission rate

Odds ratio (95% CI) = 5.8 (3.3–10.4)

*TCZ monotherapy patients from AMBITON who entered long-term extension study

Aim
To evaluate the efficacy and safety of tocilizumab monotherapy in patients from AMBITION who remained in the long-term extension study up to 240 weeks
Patient disposition

Figure 1. Retention of AMBITION patients in the LTE study receiving open-label TCZ 8 mg/kg.

- Remaining
- Withdrawn during current visit
- Withdrawn during previous visits
- Likely withdrawn

*Entry into AMBITION core study.
*Last infusion occurred >84 days before data cut.
Remission rates over time

Figure 3. Percentages of patients who achieved (A) DAS28 <2.6 (DAS28 remission) and (B) CDAI remission (CDAI ≤2.6) among patients randomly assigned to TCZ monotherapy who continued into the LTE study.
### Table 2. Withdrawals from the Study

<table>
<thead>
<tr>
<th>Reason for Withdrawal, n (%)</th>
<th>Patients Remaining on TCZ Monotherapy n = 139</th>
<th>Patients Who Added DMARDs n = 104</th>
</tr>
</thead>
<tbody>
<tr>
<td>AE/iillness</td>
<td>15 (10.8)</td>
<td>21 (20.2)</td>
</tr>
<tr>
<td>Withdraw consent</td>
<td>3 (2.2)</td>
<td>5 (4.8)</td>
</tr>
<tr>
<td>Insufficient therapy</td>
<td>1 (0.7)</td>
<td>2 (1.9)</td>
</tr>
<tr>
<td>Death</td>
<td>3 (2.2)</td>
<td>2 (1.9)</td>
</tr>
<tr>
<td>Failure to return</td>
<td>2 (1.4)</td>
<td>1 (1.0)</td>
</tr>
<tr>
<td>Refused treatment</td>
<td>4 (2.9)</td>
<td>1 (1.0)</td>
</tr>
<tr>
<td>Administrative/other</td>
<td>8 (5.8)</td>
<td>1 (1.0)</td>
</tr>
<tr>
<td>Lost to follow-up*</td>
<td>1 (0.7)</td>
<td>0</td>
</tr>
<tr>
<td>Total</td>
<td>37 (26.6)</td>
<td>32 (30.8)</td>
</tr>
</tbody>
</table>

*As of 1 April 2011.

*Last infusion occurred >84 days from data cut.
Added DMARDs included MTX (93%), hydroxychloroquine (3%), leflunomide (2%) and parenteral gold (2%)

There was no association between baseline MTX experience status and addition of a DMARD
Figure 5. Most frequent SAEs over time.
• Fifty-seven percent of AMBITION patients remained on TCZ monotherapy in this study with durable efficacy over time
• There was no association between baseline MTX experience status and addition or no addition of a DMARD
• The proportion of patients withdrawing for adverse events was higher in those who added DMARDs than in those who remained on monotherapy
• No obvious associations between SAEs and duration of TCZ exposure were observed, and no new safety signals were detected
Implications for practice

• These data reinforce the view that TCZ (and maybe tofacitinib) is the bDMARD of choice where monotherapy is required
• Unlike other bDMARDs, adding a traditional DMARD doesn’t add much in terms of efficacy and doubles the risk of adverse events.
• Efficacy of TCZ monotherapy appears to peak about 18 months so a prolonged trial may be necessary in some patients
• Clinical trial infection rates are lower than post-marketing studies so caution is necessary in the elderly, frail person plus/minus NIDDM and/or corticosteroids.